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Photoinduced Release of a Chemical Fuel for Acid-Base Operated Molecular Machines

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Abstract: Back and forth motions of the acid-base operated molecular switch **1** are photo-controlled by irradiation of a solution which also contains the photolabile prefuel **4**. The photo-stimulated deprotection of the prefuel produces controlled amounts of acid **2** whose base-promoted decarboxylation fuels the back and forth motions of the Sauvage type [2]-catenane based molecular switch. Since switch **1** and prefuel **4** do not interact in the absence of irradiation, an excess of the latter with respect to **1** can be added to the solution from the beginning. In principle, a photo-control of the back and forth motions of any molecular machine whose operation is guided by protonation/deprotonation, could be attained by use of prefuel **4**, or of any other protected acid that undergoes deprotection by irradiation with light at a proper wavelength, followed by decarboxylation under conveniently mild conditions.

Introduction

In natural systems, complex molecular architectures assembled from small and simple building blocks are able to convert energy from various sources into molecular-level directional motion, thus performing many of the useful tasks at the basis of fundamental biological processes.^[1] The extraordinary efficiency demonstrated by nature in the design of such stimuli-responsive systems has always been of inspiration for scientists in many research fields, especially in chemistry. Controlling nanoscale motion in artificial systems and interfacing them with other structures on the same scale, as well as with the macroscopic world, would potentially lead to revolutionary results influencing all of the fields of science and technology. For these reasons, although the exquisite level of complexity of natural molecular machines still appears out of reach, the design of artificial molecular machines represents an extremely attractive research topic.^[2]

Many efforts have been made towards this goal. Relatively simple, prototypal examples of stimuli responsive systems, composed either of single molecules or a limited number of components, have been designed and studied, in order to investigate how motions at the nanoscale level can be triggered and controlled. Such systems can be divided into two main

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groups depending on whether the source of energy required for the operation is light or a chemical fuel.

Light has been often chosen as a stimulus to obtain the control of both rotary and translational motion, with the advantage of producing no waste products.^[3] For example, Feringa developed a series of rotary motors based on overcrowded alkenes where a rotor performs complete 360° rotation with respect to a stator around a double bond.^[4] The whole process is powered by the repetition of a sequence of two reactions, consisting of a light induced *cis-trans* isomerization of the double bond and a spontaneous thermal relaxation step. Light powered linear motion in rotaxane-based molecular shuttles has been achieved by Leigh's group, using a nanosecond laser pulse,^[5] and by Balzani's group, using sunlight.^[6]

Nanoscale motion, both in covalent and supramolecular structures, has been also triggered and controlled by sequences of chemical reactions. Acid-base chemistry, and other reversible interactions have been widely used in rotaxane and catenane based molecular switches, albeit with many limitations concerning the lack of net directionality and the impossibility to perform autonomous motion.^[20,p] No doubt an important contribution to the resolution of both these hurdles was recently due to Leigh's group. They designed and realized a [2]-catenane in which one of the two macrocycles performed autonomous and unidirectional cycles around the other.^[7]

In the frame of chemical fuelled molecular switches, we recently reported that the Sauvage-type catenane 1 depicted in Scheme 1, undergoes back and forth motions from state A to states B (B' and **B**"), and back again to state **A**, in the presence of 1 mol equiv of 2-phenyl-2-cyanopropanoic acid 2 used as a chemical fuel. [8] While in states B the catenane-based switch possesses a well-defined co-conformation with the two phenanthroline subunits tightly held in proximity by the shared proton, state A cannot be associated to any precisely defined co-conformation. A distinctive feature of such system is that no additional antifuel is needed to restore the switch to its initial form since the transformation of the reactant 2 to the product 3 (2-phenyl-2cyanopropane) is step by step coupled to the transition $A \rightarrow B \rightarrow A$. A first proton transfer from 2 to 1 produces the proton catenate 1H⁺, which is paired to a carboxylate ion (Scheme 1, state B'). The subsequent decarboxylation step leads to state **B**", where $\mathbf{1}\mathbf{H}^{+}$ is paired to an anion in which the negative charge was suggested to be strongly localized on the nitrogen atom of the cyano group (Scheme 1, state B").^[9] A final, rate determining proton transfer from 1H⁺ to the anion, restores the catenane to its neutral form 1, giving the waste product 3. This system was of inspiration to Leigh and co-workers who recently exploited the decarboxylation reaction of trichloroacetic acid for the unidirectional operation of rotary and linear molecular motors.^[10]

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Scheme 1. Switching motions of catenane 1 fuelled by acid 2. Fast and quantitative proton transfer (step $A \rightarrow B'$) fixes the contact between the interlocked macrocycles in the region of the phenanthroline nitrogen atoms. Loss of CO₂ (step $B' \rightarrow B''$), followed by slower back proton transfer from 1H⁺ to its counteranion, restores the catenane to its original form (step $B'' \rightarrow A$).

We also demonstrated that the duration of the $A \rightarrow B \rightarrow A$ motion of **1** can be varied from minutes to days by introducing substituents in the *para* position of the phenyl group of **2**, with electron-withdrawing groups accelerating and electron-donating groups retarding the motion.^[9]

A major drawback related to the use of 2 and its derivatives as fuels for the cyclic motions of 1 lies in the impossibility to use an excess fuel with respect to the machine. Indeed, if an excess fuel is used, a mechanistic shunt is opened that consumes all of the excess acid, without the involvement of concomitant motions of the switch: if undissociated acid 2 is still present when the ion pair of state B" is completely formed, such acid will donate the proton to the anion partner in B", and 1H⁺ will remain protonated until excess acid is present. Such disadvantage poses severe limitations to an autonomous operation of the molecular switch, which does not exploit the energy supplied by the excess fuel. A possible way to overcome this problem would consist in the use of a prefuel that can be activated to release the fuel in a controlled manner. Here, the idea is to add to catenand 1 a photosensitive prefuel that is able to generate fuel 2 by irradiation with light at a properly selected wavelength.



Results and Discussion

3'5'-Dimethoxy-benzoin (DMB) was demonstrated by Corrie and Wan^[11] to be an optimal protecting group for the carboxylic

function. Such protecting group can be easily and rapidly removed by irradiating the solution according to a mechanism involving the singlet excited state of the protected carboxylic acid.^[12] Thus we envisaged that protection of acid **2** with DMB would represent a good strategy to obtain a prefuel enabling a photocontrolled release of the fuel through irradiation.

Prefuel **4** was prepared by condensation of DMB with acid **2** in the presence of dicyclohexylcarbodiimide and catalytic amounts of 4-dimethylaminopyridine.

Figure 1 shows the variations of the UV-Vis spectrum of a 0.050 mM prefuel 4 solution in dichloromethane (2 mL in 1 cm cuvette) upon irradiation centered at 335 nm. Light irradiation was performed on a spectrofluorimeter equipped with a 150 W xenon lamp (10 nm spectral bandwidth). In accordance to what observed by Corrie and Wan for other protected acids,^[11] production of fuel 2 and 1-phenyl-4,6-dimethoxybenzofuran (DMBF) from prefuel 4 (eqn 1) is a clean process as witnessed by the presence of two sharp isosbestic points (Figure 1). ¹H NMR monitoring of a more concentrated solution of 4 confirms a clean deprotection process upon irradiation at 335 nm (see Figure S1 in the SI). Once verified that the light induced production of 2 from 4 was well-working, we set the conditions for the photo-controlled back and forth motions ($A \rightarrow B \rightarrow A$) of catenane 1 which are outlined in Scheme 2.^[13]



Figure 1. Variations of UV-Vis spectrum of a 0.050 mM solution of prefuel **4** in CH₂Cl₂ at 25 °C after repeated irradiations at $\lambda = 335$ nm. The inset shows that the absorbance at 302 nm increases according to a first-order time dependence.

Figure 2 shows the UV-Vis spectra of 1, $1H^+$ (CF₃CO₂⁻ salt), 2, 4, and DMBF. In order to minimize undesirable photo-induced side

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reactions, deprotection of prefuel **4** to fuel **2** was carried out by irradiation of the solution at 335 nm. At this wavelength prefuel **4** has still a weak absorption tail (see insets in Figure 2b) and so do compounds **1**, $1H^+$ and DMBF whereas fuel **2** does not absorb at all.



Scheme 2. Photo-controlled motions of catenane 1. Irradition of prefuel 4 produces fuel 2, which in turn allows the switching of 1 from state A to states B and back again to state A.

We previously showed^[9] that the $\mathbf{A} \rightarrow \mathbf{B} \rightarrow \mathbf{A}$ motion can be followed by UV-Vis spectroscopy since the anion in state **B**" has a characteristic absorption band centered at 375 nm. This is a fortunate situation, as all of the other species do not absorb at this wavelength (Figure 2).

A reaction between 1 and 2 was initially carried out at lower concentrations with respect to the kinetic runs previously performed^[8,9] with the aim to check whether the system still works under conditions convenient for the photochemical control of the catenane 1 motions. Figure 3 compares the absorbance variation at 375 nm as a function of time related to the reaction between 0.050 mM 1 and 0.050 mM 2 with that of the same reaction carried out at higher concentrations,^[9] 0.30 mM 1 and 0.30 mM 2. Reaction times are practically unchanged confirming that the mechanism in Scheme 1 is still operating at lower concentrations. At the same time, the maximum absorbance values, reached at t ≈ 100 s in both cases, are in accordance with a complete formation of intermediate **B**ⁿ, which then disappears to give product **3** and catenane **1** in its neutral state.



Figure 2. UV-Vis spectra of: (a) 1 (blue), $1H^+CF_3CO_2^-$ (red); (b) 4 (black), 2 (pink) and DMBF (green) (CH₂Cl₂, 25 °C). The inset shows the enlargement of the absorption tail of 4.



Figure 3. UV-Vis monitoring of the reaction between 0.050 mM (a) and 0.30 mM (b, data from ref 9) equimolar **1** and **2** (CH₂Cl₂, 25 °C). Curves are plots of a standard first order equation with $k = 2.4 \times 10^{-4} \text{ s}^{-1}$ in both cases.

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Thus, a solution of 1 (0.050 mM) and a 10-fold excess of prefuel 4 (0.50 mM) was repeatedly subjected to irradiation periods at 335 nm.^[14] The result of this experiment is reported in Figure 4. In the pre-phase I, the solution is irradiated for 120 s in the spectrofluorimeter and then the cuvette is transferred into the spectrophotometer in order to follow the catenane motion. Phase I (from 120 s to about 3h) nicely reveals the back proton transfer from state B" to catenane 1 in its neutral form and waste product 3. A second pre-phase follows in which the cuvette is again transferred into the spectrofluorimeter and the solution irradiated for additional 120 s, then the second backproton transfer (phase II) is followed in the spectrophotometer up to about 6 h. The cycle is repeated two more times (phases III and IV). The fraction of catenane 1 which is observed to perform the $(A \rightarrow)B \rightarrow A$ motion can be quoted by comparison of the ΔA value at 375 nm recorded at each cycle, with the corresponding value in Figure 3a. In cycles I and II about 42% of catenane 1 molecules are observed to move from state B" to state A. which implies the operation of the whole motion $A \rightarrow B \rightarrow A$.^[15] Such fraction somewhat decreases in the subsequent cycles III and IV.



Figure 4. UV-Vis monitoring of 0.050 mM 1 in the presence of 0.50 mM prefuel 4 after 120 s of irradiation of the solution at time 0, 10920, 21840 and 32760 s at 335 nm (CH₂Cl₂, 25 °C). The black horizontal bar corresponds to a 42% conversion of state A into state B".

Production of the two waste products **3** and DMBF from photodeprotection of prefuel **4** in the presence of catenane **1** was also verified by ¹H NMR spectroscopy. A 2.0 mM equimolar solution of **1** and **4** (2 mL in 1 cm cuvette) was irradiated at 335 nm for 1 h. Comparison of the ¹H NMR spectrum of the crude product with that of a typical catenane **1** promoted decarboxylation of **2** and of an authentic sample of DMBF (Figure S2) showed the production of both waste products **3** and DMBF. Half of the initial amount of prefuel **4** appears to have been consumed under these conditions.

To sum up, the photo-controlled motion of catenane **1** has been achieved. Initially, a 10-fold molar excess of prefuel was added and the fuel release was gradually controlled by irradiation of the solution at the proper wavelength. Each time the fuel was liberated a fraction of the catenane molecules underwent a complete $\mathbf{A} \rightarrow \mathbf{B} \rightarrow \mathbf{A}$ cycle.

Our attempts to increase the fraction of the catenane molecules undergoing the back and forth motions were frustrated by unavoidable difficulties intrinsically dependent on the nature of switch 1. As expected, when irradiation times were lowered from 120 to 60 s, the observed percentage of catenane 1 undergoing back and forth motions between states A and B decreased from about 42% to about 20-25% (see Figure S4). On the other hand, when the irradiation time per cycle was increased to 180 s, during the first two cycles almost 60% of catenane molecules were observed to undergo the motions but, unfortunately, in the subsequent cycles such fraction strongly decreased (Figure S5). The decrease in efficiency in subsequent cycles was even more marked when an irradiation time per cycle as high as 300 s was applied (see Figure S6). In this case, during the first cycle almost 70% of the catenane molecules were observed to perform the back and forth motion while the percentage was practically halved during the second cycle.



Figure 5. UV-Vis spectra of (a) 0.010 mM 1 and (b) 0.010 mM $1H^+CF_3CO_2^-$ after 0 (black), 5 (red), 10 (green), 15 (blue), 20 (pink), and 25 (cyano) min irradiation at 335 nm (CH₂Cl₂, 25 °C).

In order to shed light on the origin of the loss of efficiency of the back and forth motions of catenane 1 on increasing the number of cycles, the behavior of 1 under irradiation conditions was investigated. Figure 5a reports the variations of the absorbance of a 0.010 mM 1 solution in dichloromethane upon 5 subsequent irradiations for 5 minutes each at 335 nm. From comparison of Figure 5a with Figure 2a and particularly from the presence of the sharp isosbestic point at 275 nm in both of the figures, it appears evident that irradiation causes transformation of 1 into its protonated form 1H⁺. In contrast, the spectra related to 1H⁺CF₃CO₂⁻ recorded under similar conditions (Figure 5b) do not show significant variations, even after long irradiation times (25 min). ¹H NMR analysis of a 0.20 mM solution of **1** in dichloromethane subjected to a prolonged irradiation (2 h) at 335 nm led to the same conclusion as shown in Figure 6. Protonation of 1 is indeed well evidenced by the insurgence of the typical signals in the high field region (1-0 ppm), of the triplet at 2.4 ppm, and of the signals related to the protonated phenanthroline core at low fields. As a matter of fact such signals, although to a minor extent, were already evident in the ¹H NMR spectrum of the crude product reported in Figure S2 (bottom trace). As regards to the proton source, we stress that all of the dichloromethane samples used throughout this work were flushed through basic alumina just before use, and that ¹H NMR spectra of catenane **1**, which has been previously demonstrated to be an exceedingly strong base ($pK_a > 16^{[8]}$) because of topological reasons,^[8,16] never revealed the presence of even minute amounts of 1H⁺. Thus, whatever the nature of the proton source, it should not be acidic enough to protonate the strongly basic 1. Balzani, Sauvage and coworkers^[17] reported that the basicities of the singlet excited states of phenanthroline and its 2,9-diphenyl and 2,9-dianisyl derivatives are much higher than those of the corresponding ground states ($\Delta p K_a$ of about 5, 8 and 14 in the given order). If a similar effect also operates with catenand 1, the basicity of its excited state could be enhanced to such an extent that proton abstraction from the dichloromethane solvent becomes feasible. However, an alternative possibility is that protonation of the excited state of 1 is due to trace amounts of an undetected impurity cannot be ruled out. Thus, independent of the precise nature of the proton source, the photoinduced transformation of 1 to $1H^+$ causes a loss in efficiency on increasing the number of cycles. However, because inspection of Figure 5 indicates that this effect is relatively small, the build-up of products that absorb the irradiation light could be a concomitant cause of the reduced photoconversion on successive cycles.



Figure 6. ¹H NMR (CD₂Cl₂) spectrum of 1 (bottom), 1 subjected to 2 h irradiation centered at 335 nm (middle), $1H^+CF_3CO_2^-$ (top). Signals from 8.6 to 7.2 ppm are due to aromatic protons, signals from 5.8 to 5.2 ppm are due to double bond protons, signals from 3.3 to 0 ppm are due to methylene chain protons (see ref 18a for details).

Conclusions

In this paper we have shown that it is possible to photochemically control the chemically fuelled back and forth motions of a molecular switch. In our system a light pulse converts a first molecular species (prefuel) into a second one (fuel) which, in turn, causes the large amplitude motions of a molecular switch, as a results of a cascade effect typical of biochemical systems. The main actor of such photocontrol is not the acid-base operated molecular machine 1 but prefuel 4, which can be transformed into the active fuel 2 at will by irradiation of the solution at the proper wavelength. Since switch 1 and prefuel 4 do not interact in the absence of irradiation, an excess of prefuel with respect to switch can be added to the system from the beginning. The drawbacks related to the loss of efficiency on increasing the number of motion cycles are due to intrinsic properties of the molecular switch at hand and do not spoil the generality of the principle. Control of the motion of any molecular switch or motor that moves between two (or more) states under the influence of protonation/deprotonation, could be attained by use of prefuel 4, or any other protected acid that undergoes deprotection by irradiation with light at a proper wavelength, followed by decarboxylation under conveniently mild conditions.

Experimental Section

Instruments and Methods

¹H NMR spectra were recorded on a 300 MHz spectrometer. The spectra were internally referenced to the residual proton signal of the solvent at 5.30 ppm for spectra recorded in CD₂Cl₂ and 7.26 ppm for spectra recorded in CDCl₃. Spectrophotometric measurements were carried out on a diode array spectrophotometer equipped with a thermostatted cell

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compartment. Irradiations were carried out on a spectrofluorimeter equipped with a 150 W xenon lamp, setting the λ_{exc} at 335 nm and a spectral bandwidth of 10 nm and using 2 mL quartz cuvettes with optical path of 1 cm.

Materials

All reagents and solvents were purchased at the highest commercial quality and were used without further purification, unless otherwise stated. CH₂Cl₂ and CD₂Cl₂ were flushed through basic alumina immediately prior to use. Catenane **1** and acid **2** (mixture of *EE*, *EZ* and *ZZ* geometrical isomers) were available from a previous investigation.^[8,18] DMB and DMBF was prepared as reported in the literature (see SI).^[11,19]

1-(3',5'-Dimethoxyphenyl)-2-oxo-2-phenylethyl-2-phenyl-2cyanopropanoate (4).

4-Dimethylaminopyridine (DMAP) (34 mg, 0.28 mmol), dicyclohexylcarbodiimide (DCC) (137 mg, 0.66 mmol), acid **2** (100 mg, 0.57 mmol) and DMB (466 mg, 1.7 mmol) were dissolved in CH₂Cl₂ (15.0 mL) in the given order at 0 °C. The solution was held at 0 °C under stirring for 2.5 h, then the dicyclohexylurea developed during the reaction was removed by filtration. The solution was washed with aqueous HCl (0.6 M) and subsequently with saturated NaHCO₃. The resulting organic phase was then dried, evaporated and the crude wax was subjected to chromatography (SiO₂, hexane / dichloromethane 1:6). Prefuel **4** (104 mg, 0.24 mol) was obtained as a pale yellow oil (42% yield).

¹H NMR (300 MHz, 25°C, CDCl₃): attention, prefuel **4** was obtained as a 1:1 mixture of diasteroisomers, each present as a couple of enantiomers. δ=7.92 (m, 1H), 7.83 (m, 1H), 7.60-7.32 (m, 7H), 6.70 (s, 1H), 6.68 (s, 1H), 6.55 (m, 1H), 6.52 (m, 1H), 6.39 (bs, 1H), 3.72 (m, 6H), 2.04 ppm (m, 3H). ¹³C NMR (75 MHz, 25°C, CD₂Cl₂) δ: 192.3, 192.1, 167.6, 167.3, 161.0, 135.1, 134.9, 134.3, 134.2, 134.0, 133.6, 133.5, 129.01, 128.96, 128.84, 128.80, 128.73, 128.68, 128.62, 128.5, 126.0, 119.07, 118.92, 106.0, 105.7, 101.25, 101.20, 79.8, 79.6, 55.3, 48.3, 48.2, 25.0, 24.7 ppm. UV-Vis (CH₂Cl₂): λ_{max} (ε) = 241 nm (8900), 282 nm (1552 mol⁻¹ dm³ cm⁻¹). MS (EI) *m/z* 429 [M⁺], 324 [M-105]⁺, 256 [M-173]⁺, 165 [M-264]⁺, 130 [M-199]⁺, base peak 105, 77.

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Keywords: Chemical Fuels • Molecular Motions • Photochemical Control • Catenane • Molecular Machines

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- [13] The mechanism of photodeprotection proposed by Corrie and Wan (ref 11) involves a heterolytic cleavage of the C–O bond from an intramolecular exciplex characterized by a charge transfer interaction between the methoxybenzene ring and the electron-deficient oxygen of the n, π^* singlet excited acetophenone, leading to the formation of a carboxylate and a cation precursor of DMBF. Fast deprotonation of the cation by the carboxylate produces DMBF and the carboxylic acid. Thus protonation of catenand 1 might involve either fuel 2 or the cation precursor of DMBF. In both cases the same states **B** of Scheme 1 are formed.
- [14] When non-irradiated a solution of 0.050 mM 1 and 0.50 mM 4 in CH_2Cl_2 at 25 °C remains stable for days.
- [15] In an irradiation experiment in which the transfer of the cuvette from the spectrofluorimeter to the spectrophotometer was particularly rapid it was possible to follow both the increase and decrease of the absorbance at 375 nm due to the appearance and the disappearance of the intermediate state B" (see Figure S3).
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Photocontrol of the back and forth motions of a molecular switch is attained by use of an inactive prefuel, which is at will transformed into the active form by irradiation with light at the proper wavelength.

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Photoinduced Release of a **Operated Molecular Machines**

